



# **Ion channels and properties of large neuronal networks: a computational study of re.nal waves during development**

D Karvouniari, Lionel Gil, Olivier Marre, Serge Picaud, Bruno Cessac

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# Ion channels and properties of large neuronal networks: a computational study of retinal waves during development.

D. Karvouniari, Biovision team, INRIA and LJAD, UCA

L. Gil, INLN, Sophia Antipolis

O. Marre, Institut de la Vision, Paris

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B. Cessac, Biovision team, INRIA, Sophia Antipolis



# Ion channels and properties of large neuronal networks: a computational study of retinal waves during development.

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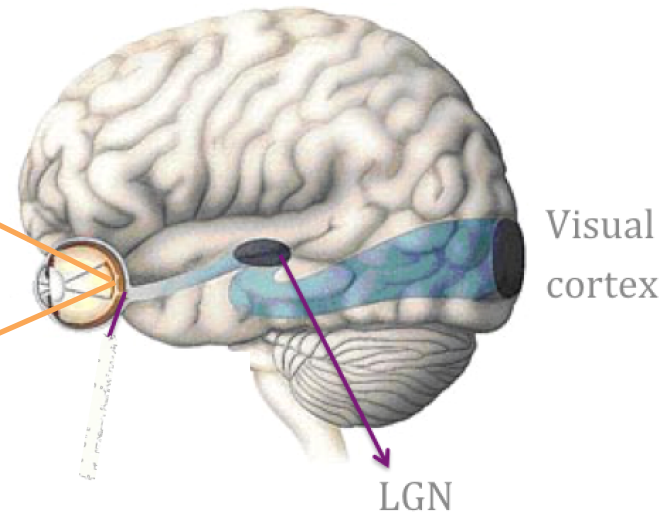
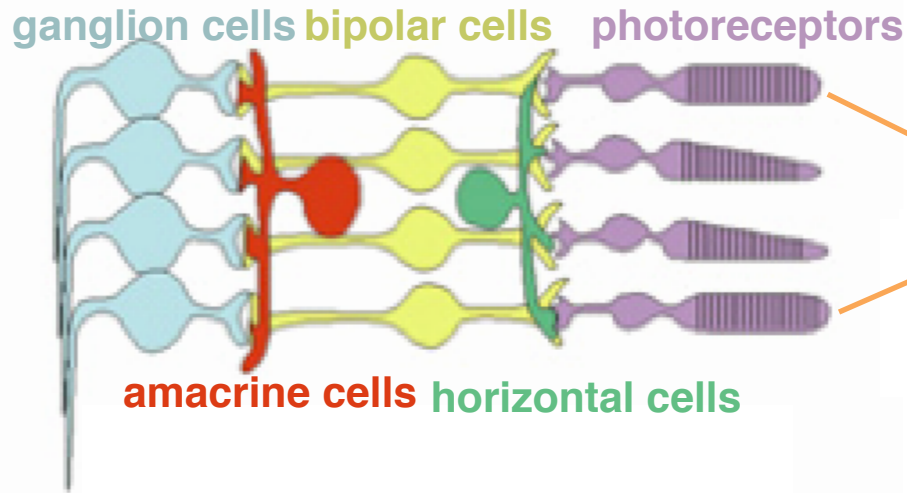
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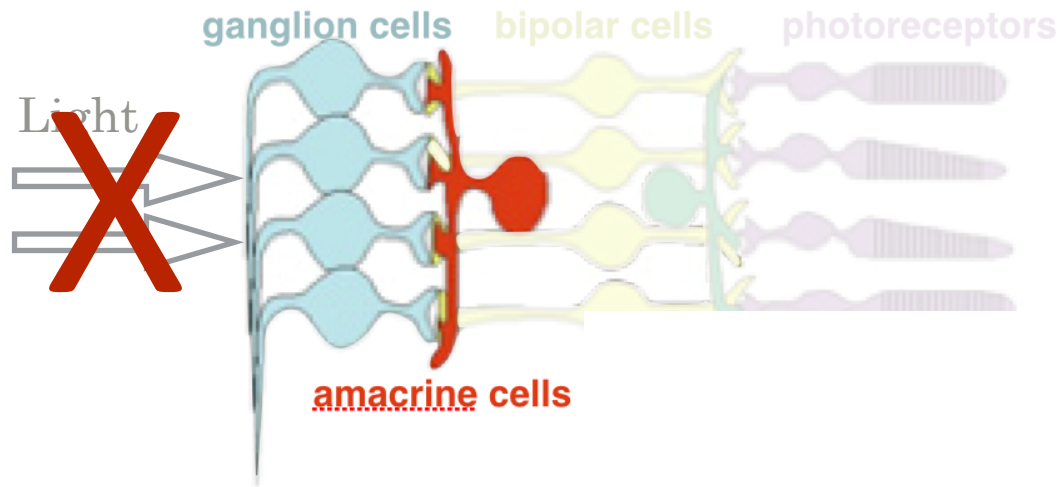
# The structure of the adult retina

## Retina's layered structure



# The structure of the retina during development

Retina's layered structure  
is shaped during development



But How?

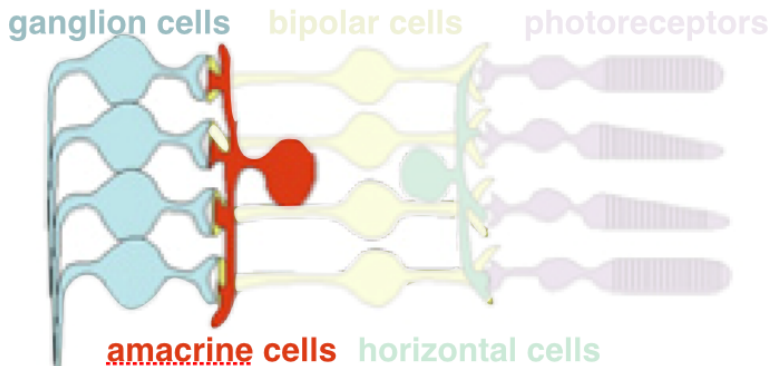


Retinal waves!

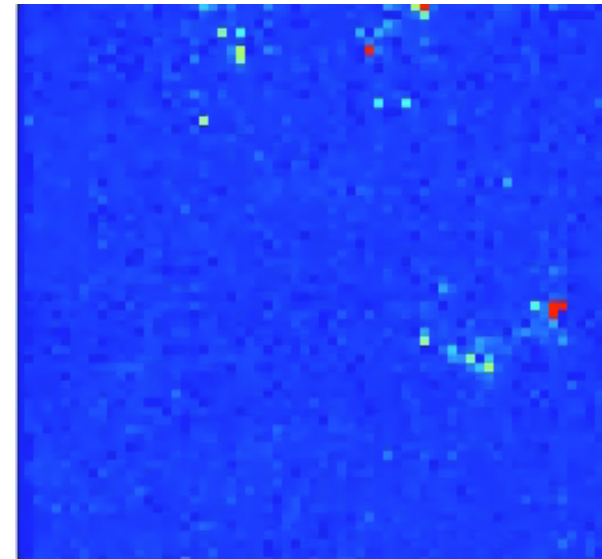
# Retinal waves

Spontaneous spatio-temporal waves during development  
Disappear short after birth  
when vision is functional

Recordings from the retina



**Multi-electrode  
array  
(MEA)**



*(Maccione et al. 2014)*

*MEA recording of the voltage from  
a P11 mouse retina in the presence  
of 10  $\mu$ M bicuculline.*

# Stages of Retinal Waves During Development

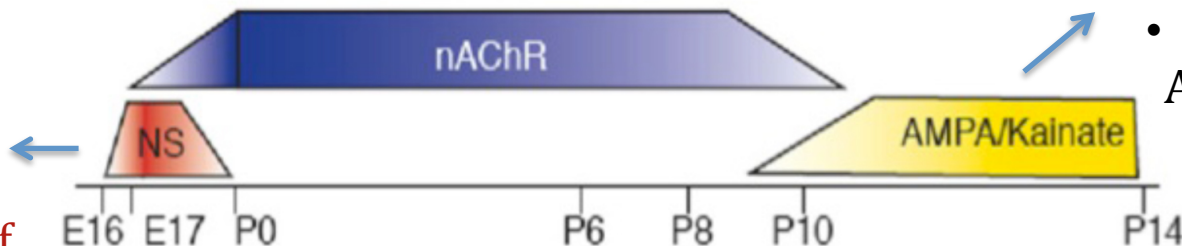
## Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)

## Stage III

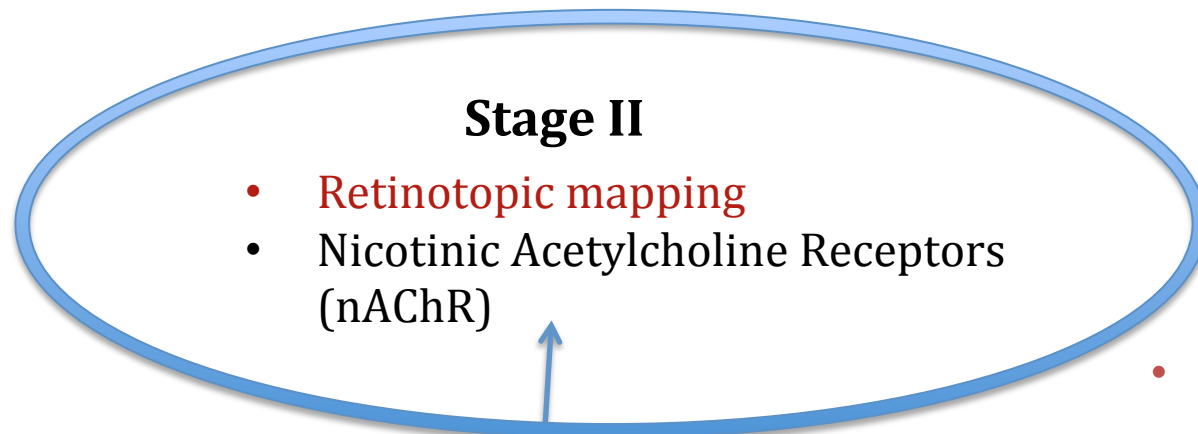
- Disappear when vision is functional
- Glutamate – AMPA receptors

## Stage I



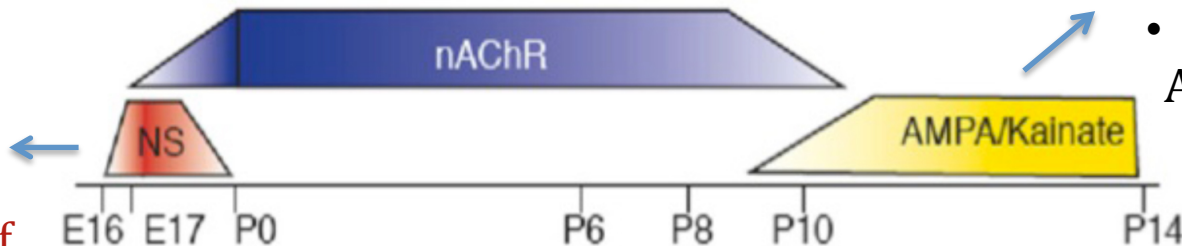
- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

# Stages of Retinal Waves During Development



- Stage III**
- Disappear when vision is functional
  - Glutamate – AMPA receptors
- 

**Stage I**



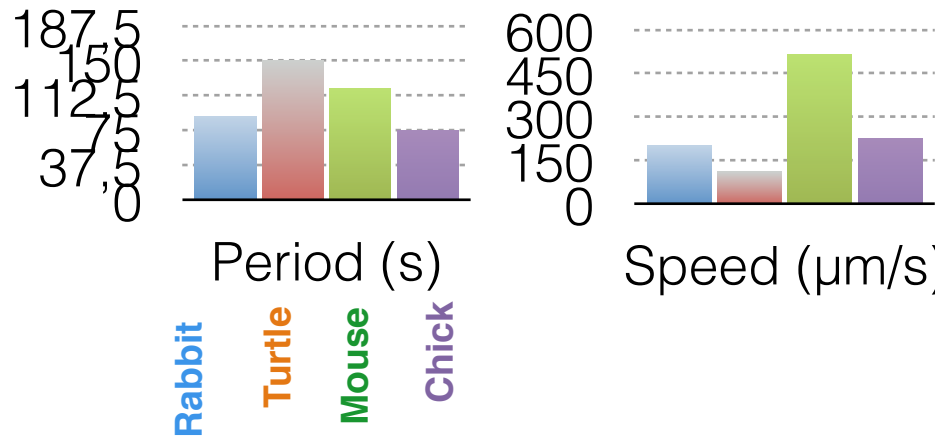
- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated



# Variability within retinal waves

## i) Across species

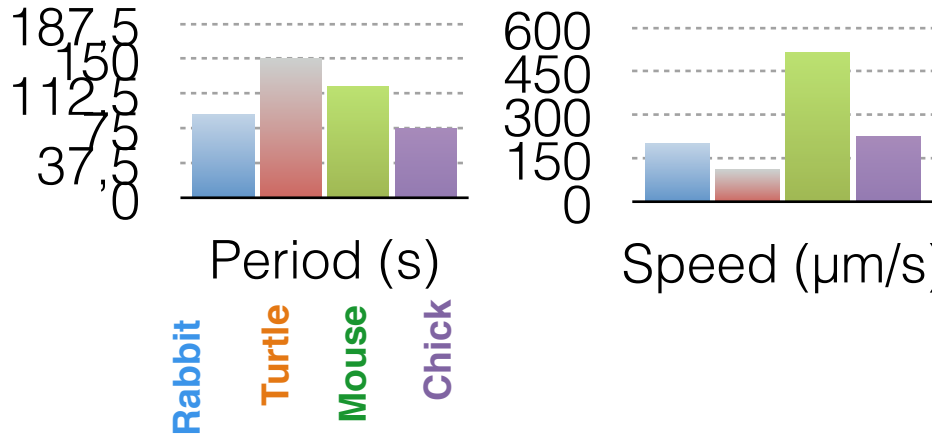
Godfrey et al. 2007



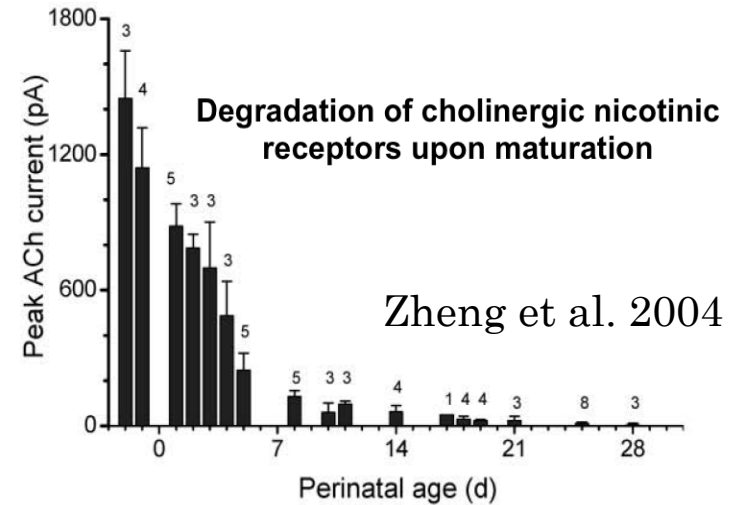
# Variability within retinal waves

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Godfrey et al. 2007



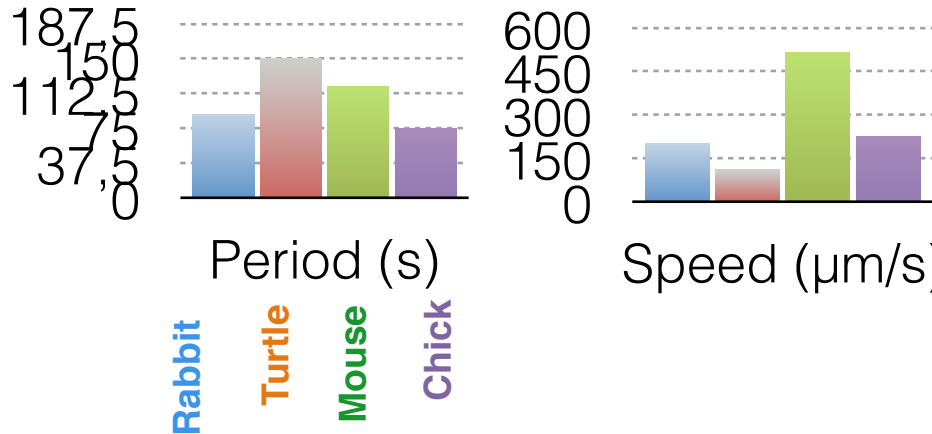
## ii) Development



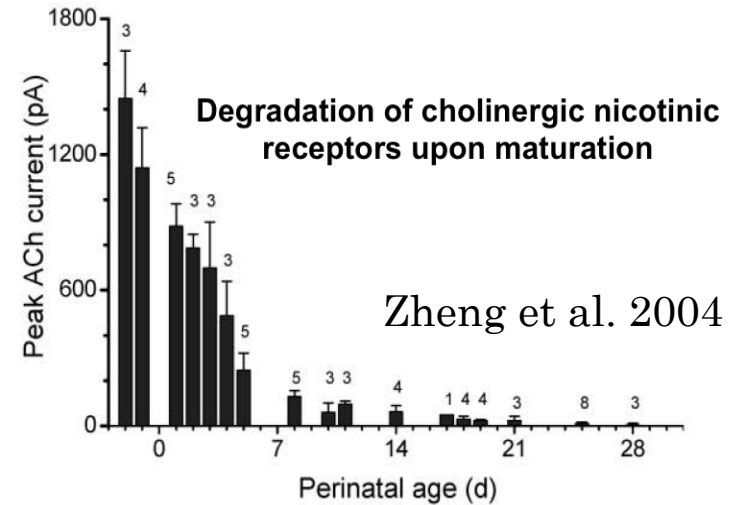
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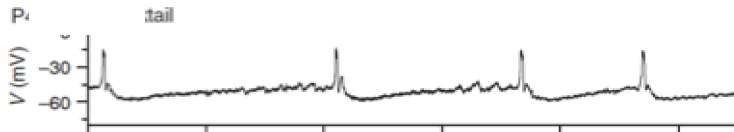


## ii) Development

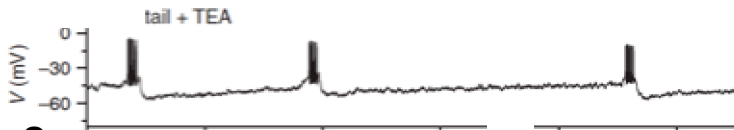
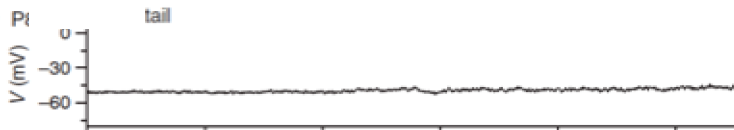


## iii) Pharmacology

P4



P8

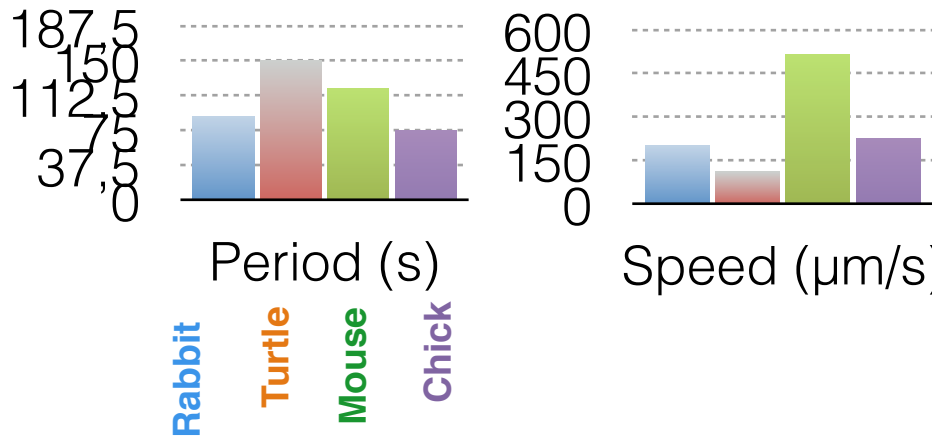


0 Time (sec) 50

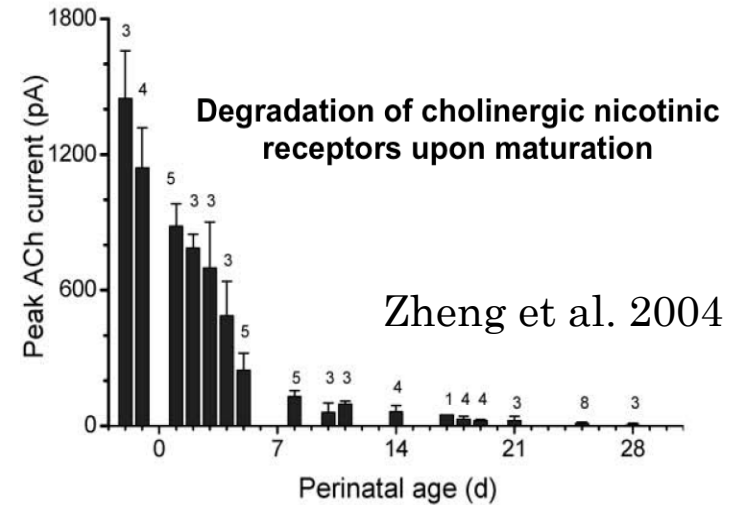
# Variability within retinal waves

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Godfrey et al. 2007

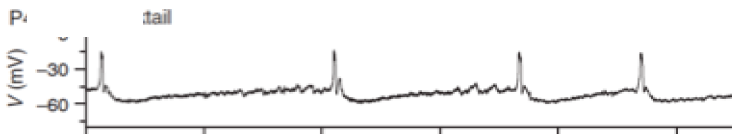


## ii) Development

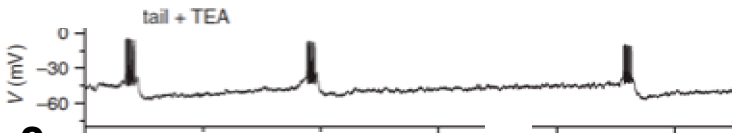
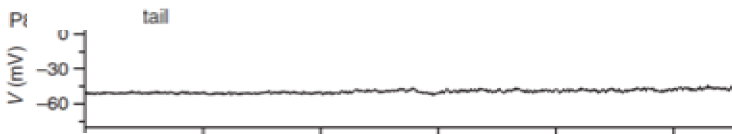


## iii) Pharmacology

P4

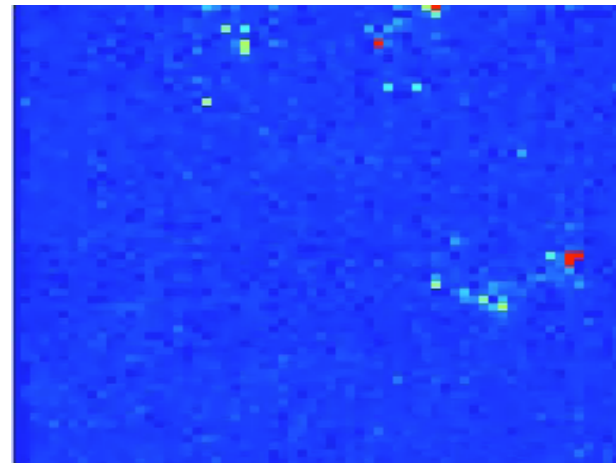


P8



0 Time (sec) 50

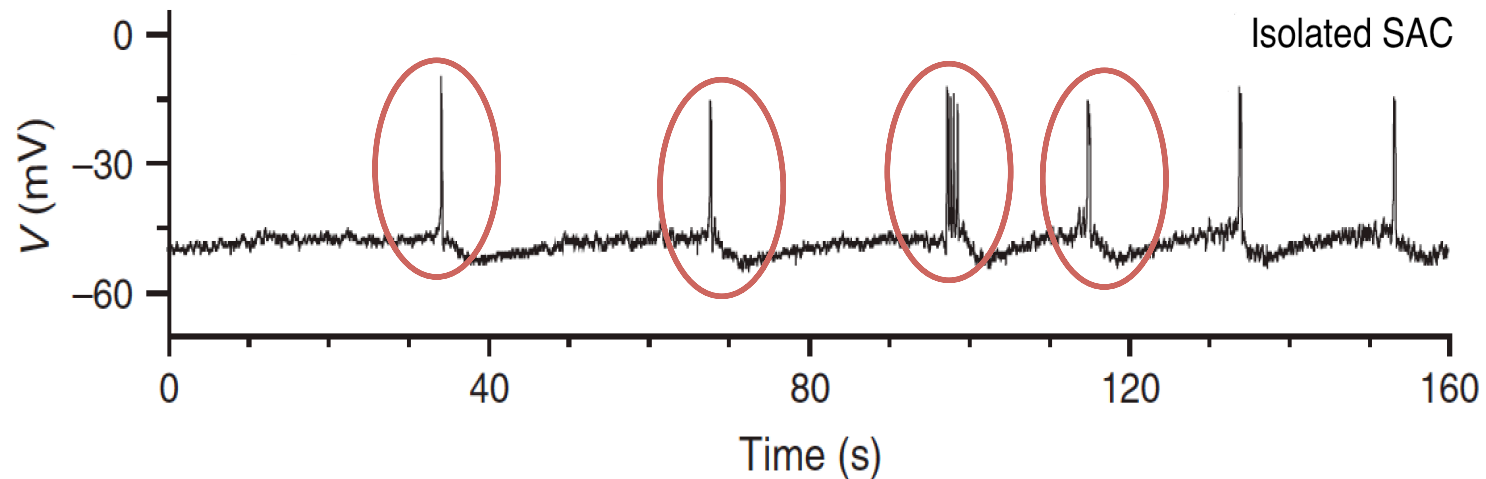
## iv) Spatial Variability



# Experiments for the emergence of retinal waves

Retinal waves require three components:

i) Spontaneous bursting activity

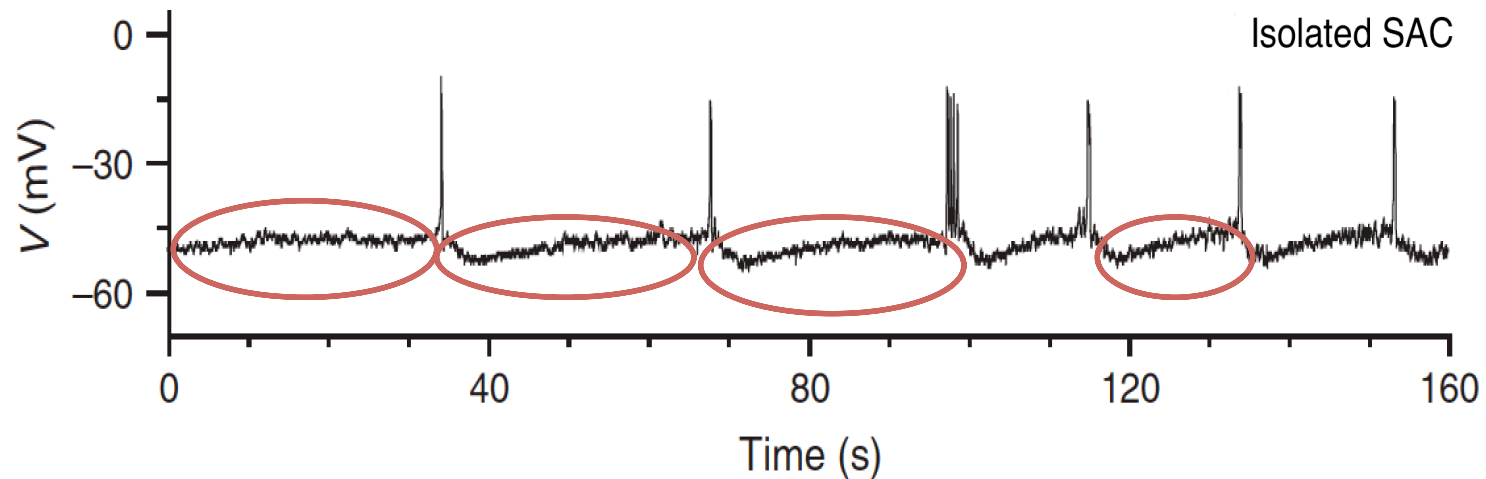


Experiment for isolated neurons,  
Zheng et al., 2006, Nature

# Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity
- ii) Refractory mechanism (slow After HyperPolarisation- sAHP)

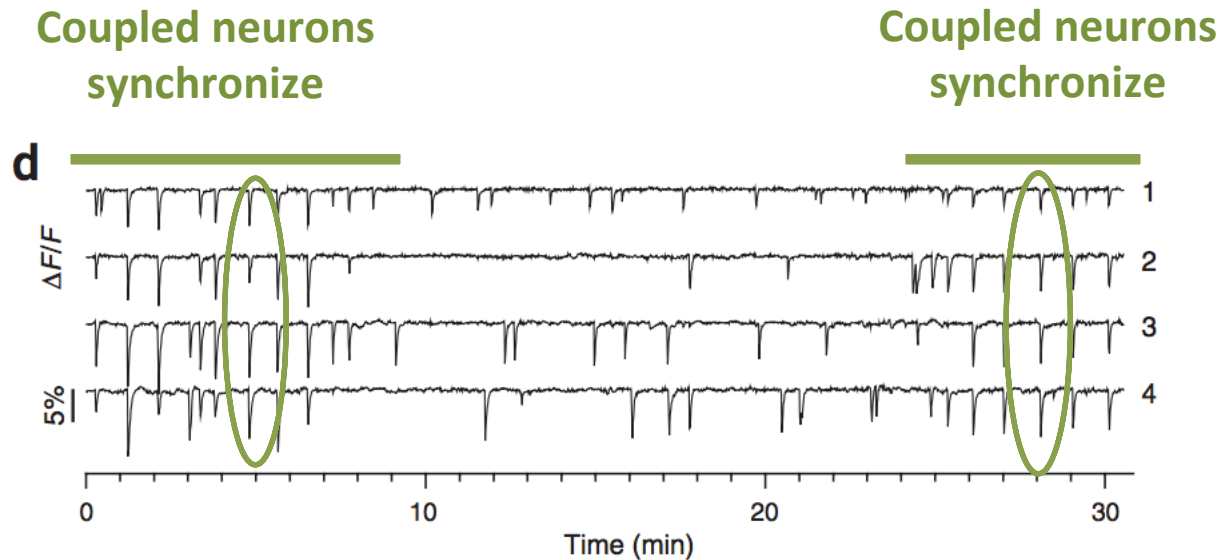


Experiment for isolated neurons,  
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# Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity
- ii) Refractory mechanism (slow After HyperPolarisation- sAHP)
- iii) Coupling (through Acetylcholine neurotransmitter)

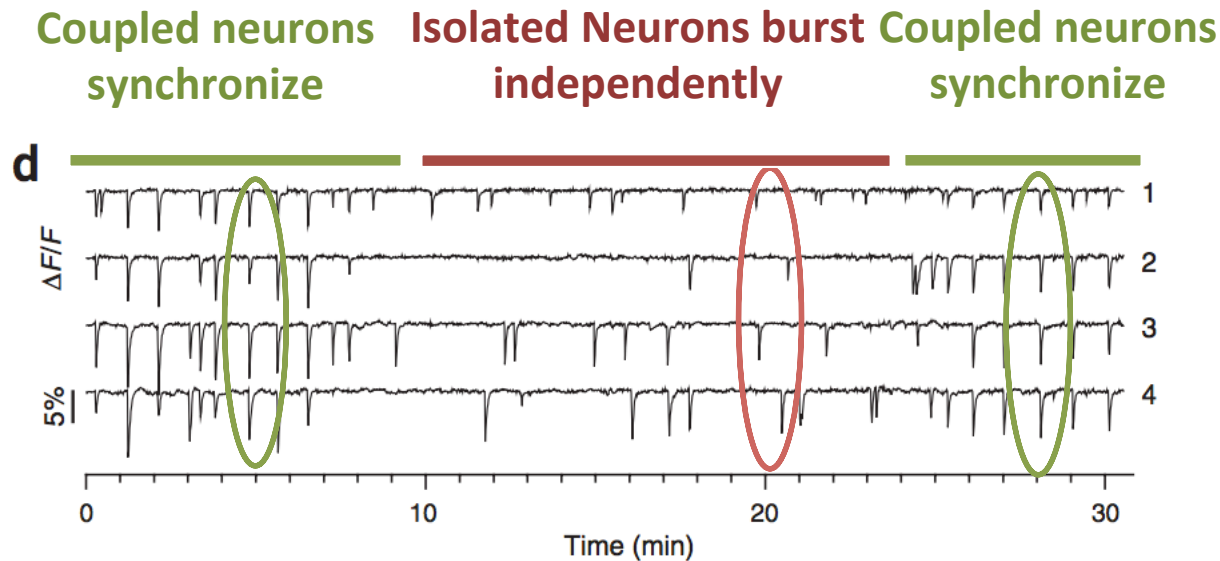


Experiment for coupled and isolated neurons, Zheng et al., 2006, Nature

# Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity
- ii) Refractory mechanism (slow After HyperPolarisation- sAHP)
- iii) Coupling (through Acetylcholine neurotransmitter)



Experiment for coupled and isolated neurons, Zheng et al., 2006, Nature



# Why study retinal waves?

## Strategy:

*To propose a model (i) sufficiently close from biophysics to explain and propose experiments and (ii) sufficiently well posed mathematically to analyse its dynamics upon varying biophysical parameters (development - pharmacology).*

- Modelling one cell bursting
- Modeling cells coupling
- Modelling waves generation, propagation and termination.

# Why study retinal waves?

## Strategy:

*To propose  
its*

Multiscale modelling

*and  
analyse  
t -*

From ionic channel to neuron to retina scale

Non linear dynamics, dynamical systems theory,  
statistical physics.

- Modelling cells coupling
- Modelling waves generation, propagation and termination.

# Main assumption

There are a few physiological parameters controlling retinal waves dynamics, evolution and variability.

Find these parameters from a mathematical analysis

Bifurcation theory

# **A network model for stage II retinal waves**

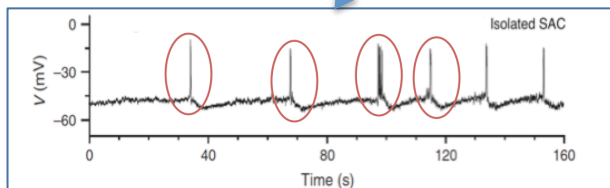
# A network model for stage II retinal waves

## Membrane potential dynamics

$$C_m \frac{\partial V}{\partial t} = -g_L^M (V - V_L) - g_{Ca}(V)(V - V_{Ca}) - g_K N (V - V_K)$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N)$$

**Morris-Lecar &  
Fast K<sup>+</sup> channels**



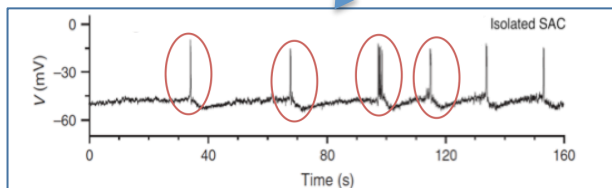
# A network model for stage II retinal waves

## Membrane potential dynamics

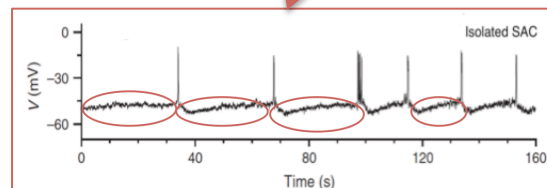
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca} (V_i) (V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K)$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V) (N_\infty(V) - N)$$

**Morris-Lecar &  
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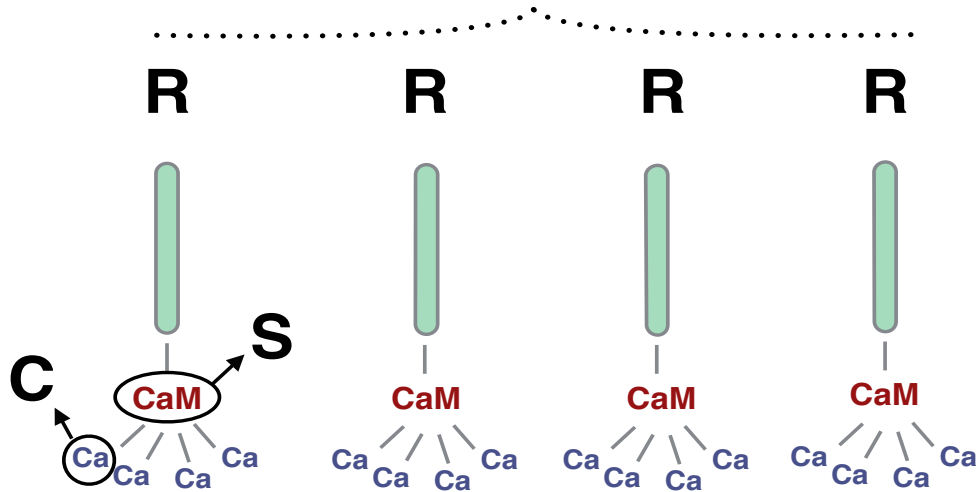


**sAHP current  
Refractory  
mechanism**



# Set of equations for sAHP current

## Activated Ca-gated K<sup>+</sup> channel



## Gating mechanism

All 4 subunits R of the channel are bound to activate the channel



Saturated Calmodulin molecule (CaM) bind to each channel subunit



4 Calcium ions bound to each saturated Calmodulin complex S

# SACs Network

## Model synaptic interactions

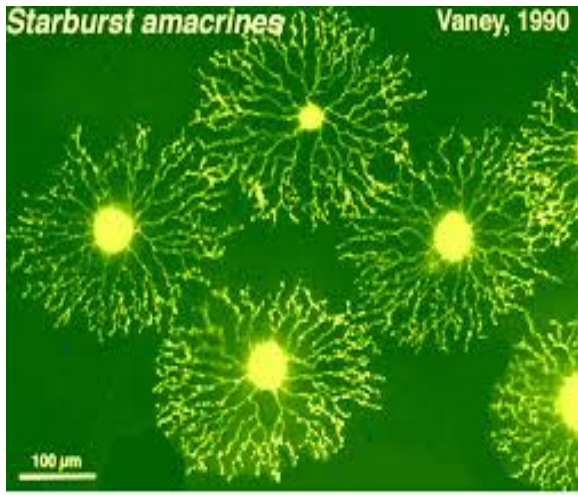
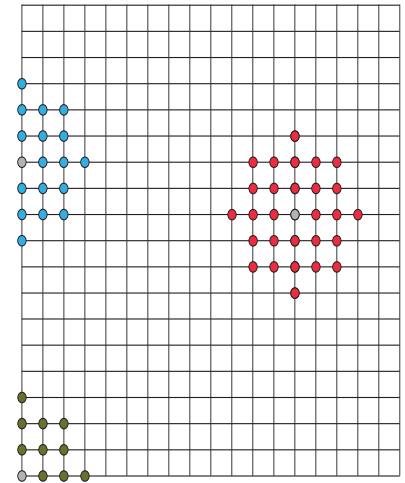
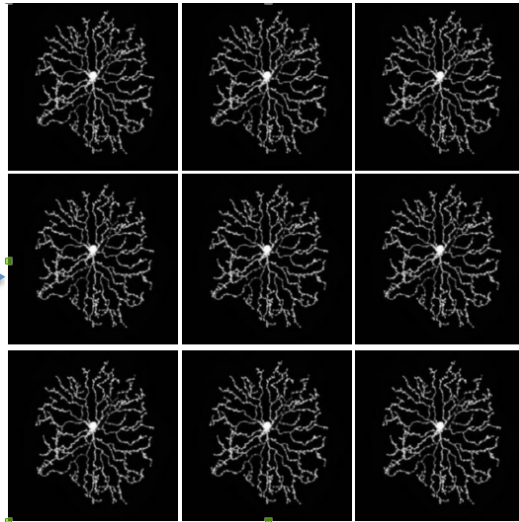


Fig 7. Starburst amacrine cells are stained with lucifer yellow in whole-mount rabbit retina.



SACs realistic  
connections

SACs on a lattice

SACs become points on  
a lattice



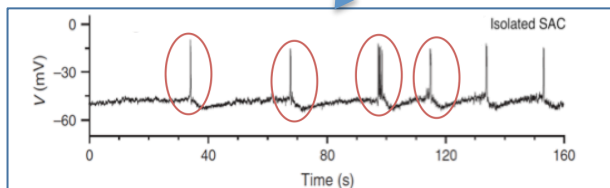
# A network model for stage II retinal waves

## Membrane potential dynamics

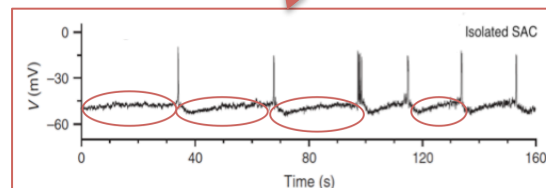
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca} (V_i) (V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K) - \sum_j g_{j,Ach} (A_j) (V_i - V_{Ach})$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V) (N_\infty(V) - N)$$

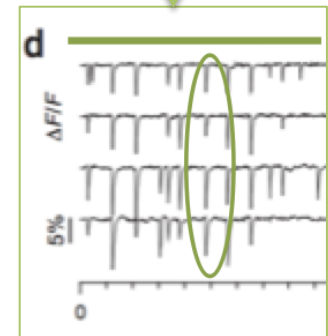
**Morris-Lecar &  
Fast K<sup>+</sup> channels**



**sAHP current  
Refractory  
mechanism**

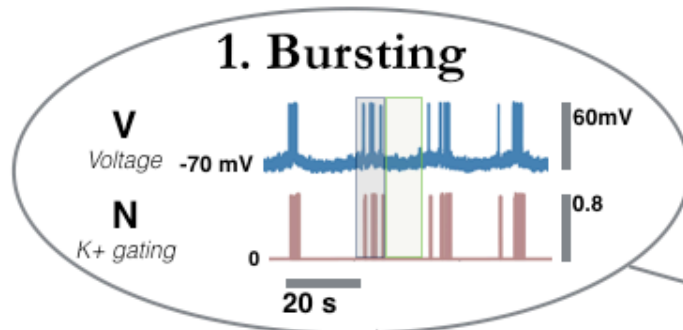


**Ach current  
Network  
effect**

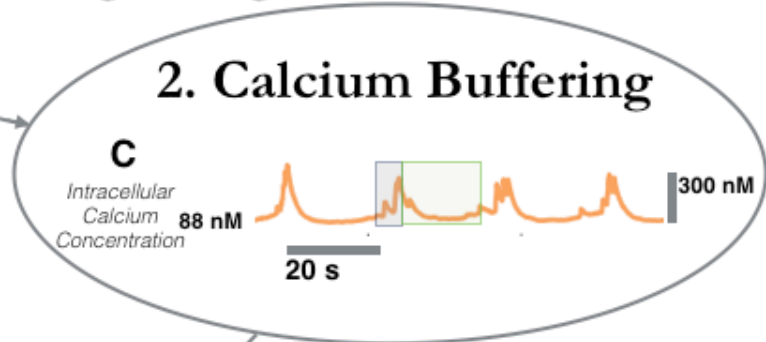


# Spontaneous Bursting Mechanism of SACs

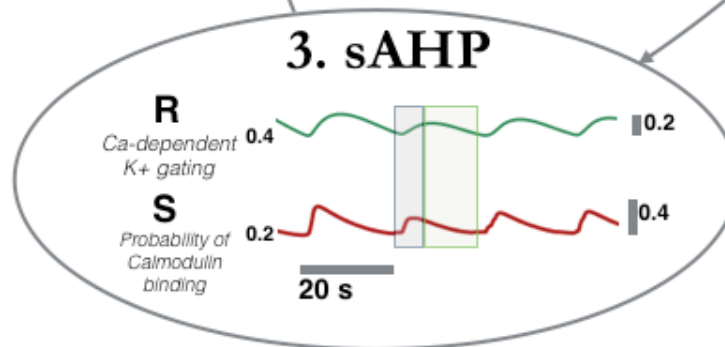
Bursting  
 sAHP



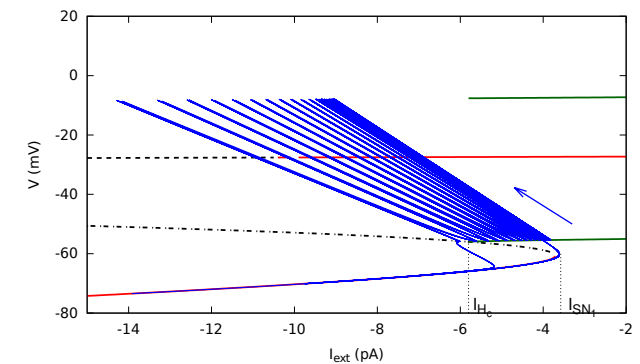
Increase of Calcium load during bursting



Bursting starts again when the Calcium load is low enough



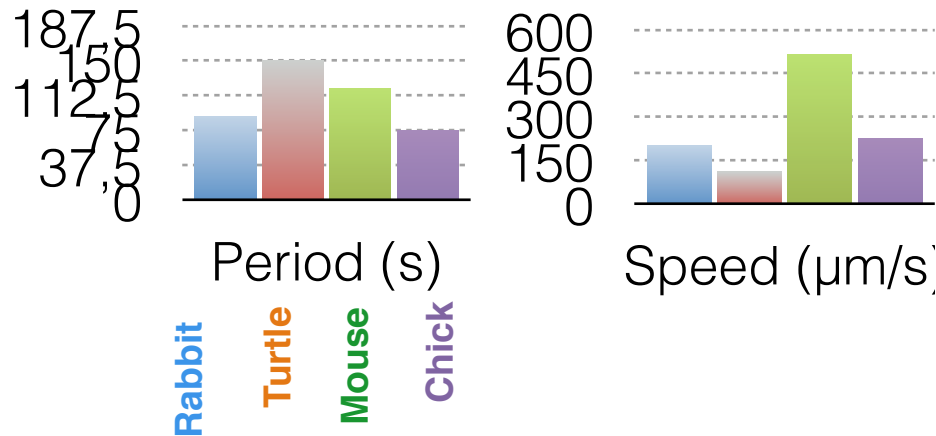
Calcium controls the sAHP phase. Voltage is low and Calcium starts offloading



# Variability within retinal waves

## i) Across species

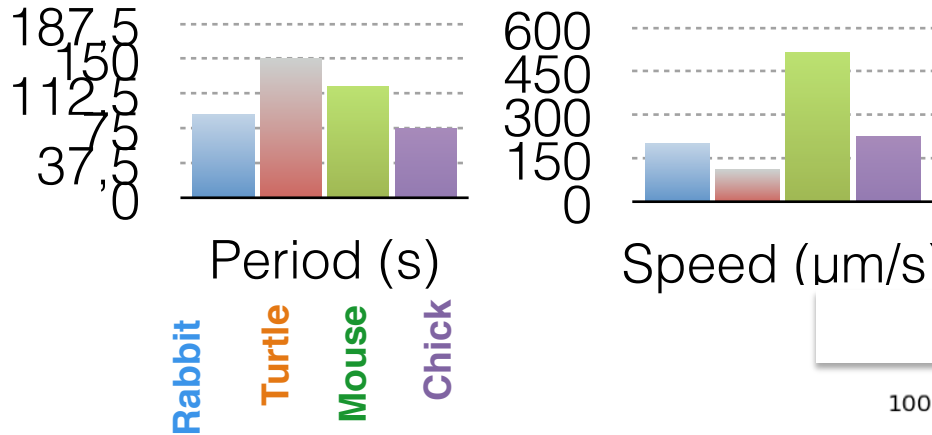
Godfrey et al. 2007



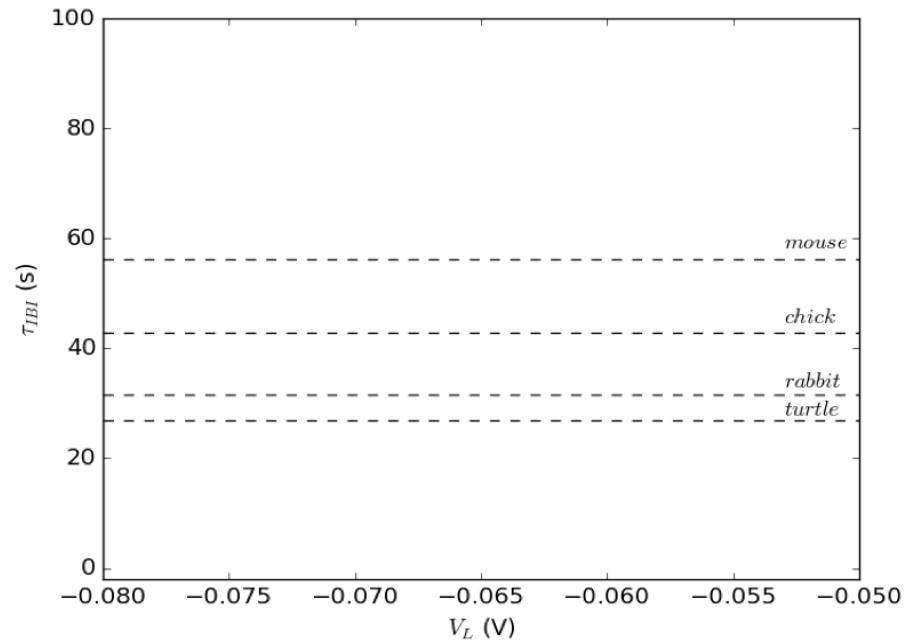
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## i) Across species

Godfrey et al. 2007



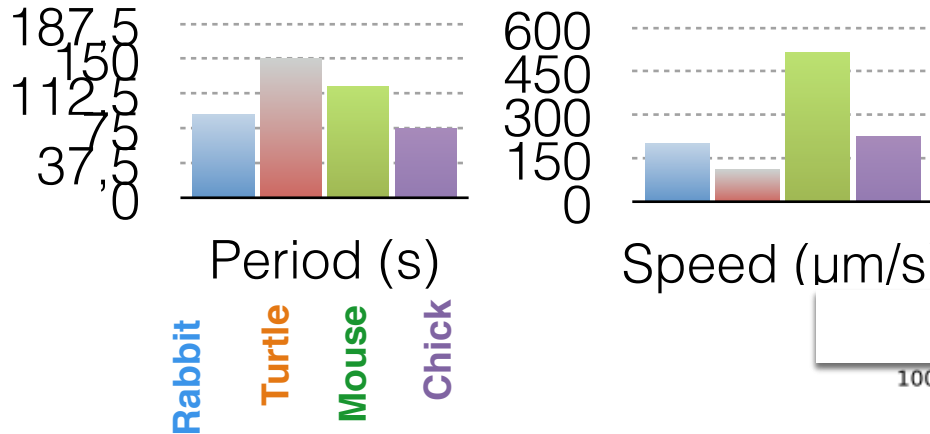
## Interburst intervals



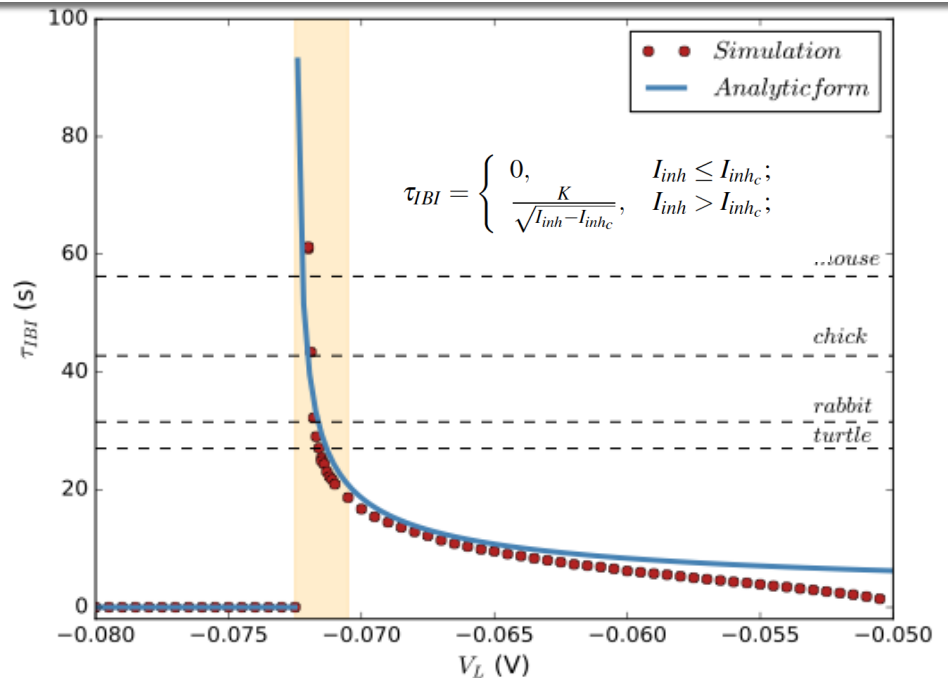
# Variability within retinal waves

## i) Across species

Godfrey et al. 2007



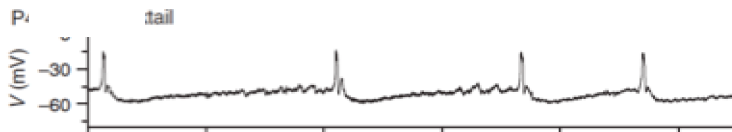
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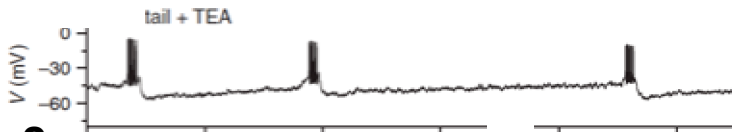
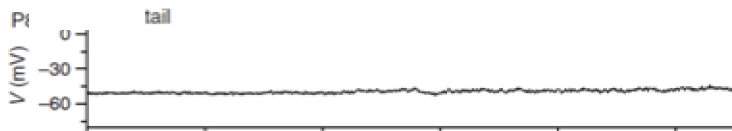
# Variability within retinal waves

## iii) Pharmacology

**P4**



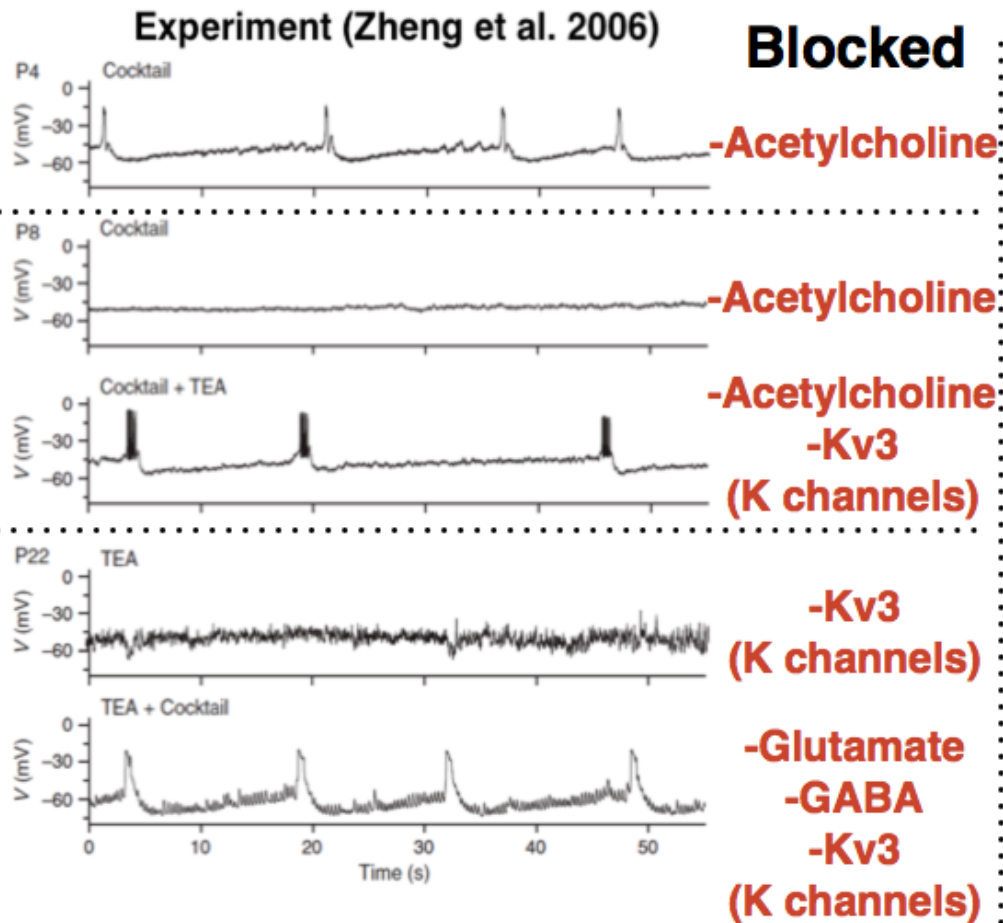
**P8**



0 Time (sec) 50

# How do SACs lose their excitability?

**A**



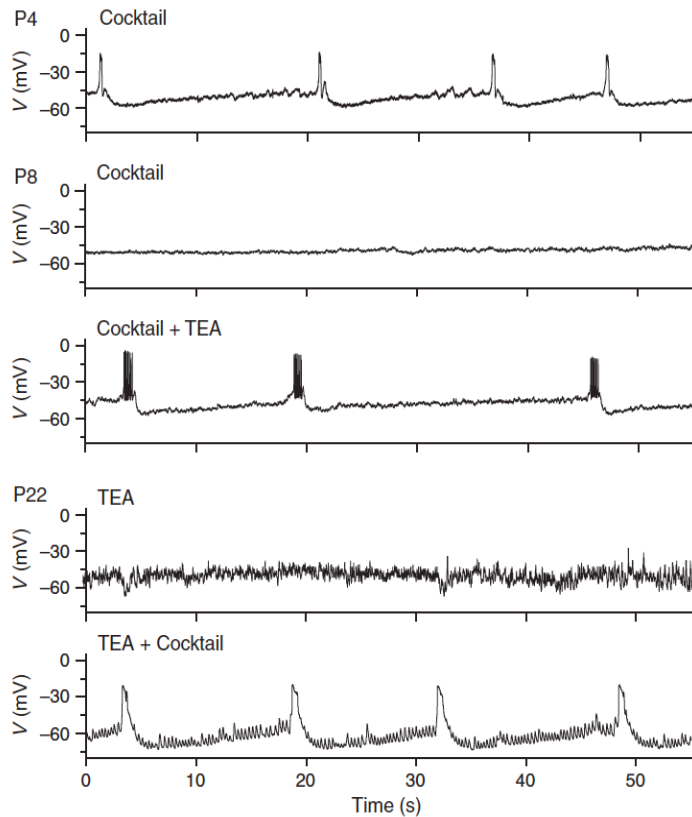
**Potassium channels  
(potentially Kv3)  
are modelled by 3  
parameters  
gK, V3, V4**

**\*TEA blocks Kv3 channels**

# Predict the role of Kv3 channels in the loss of SACs excitability

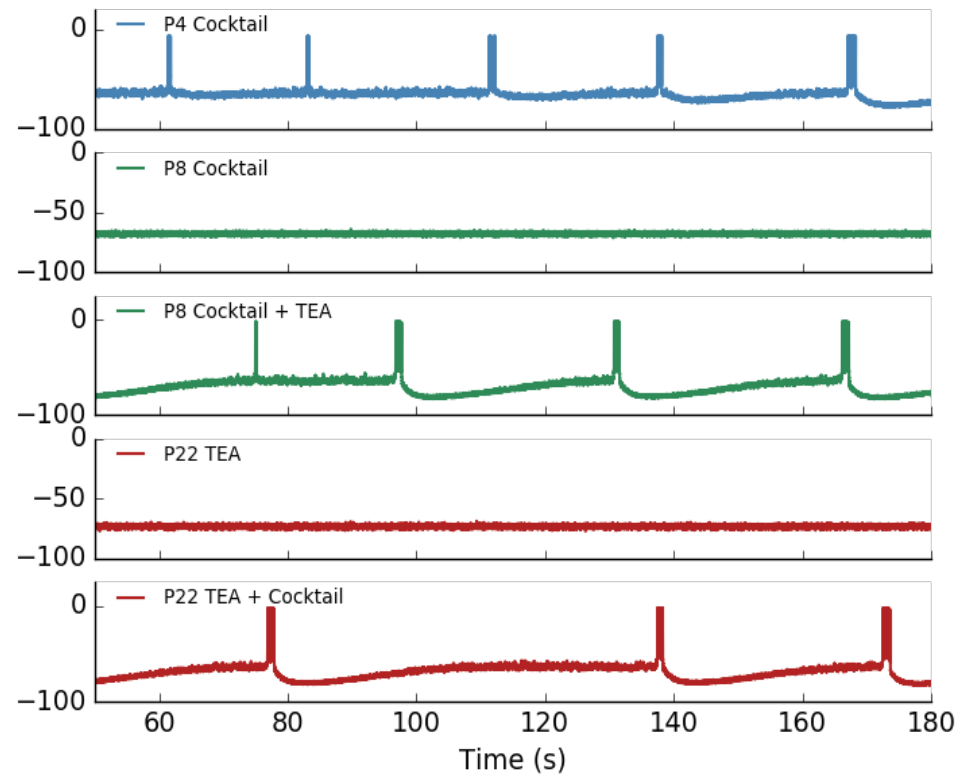
**A**

**Experiment (Zheng et al. 2006)**



**B**

**Model**

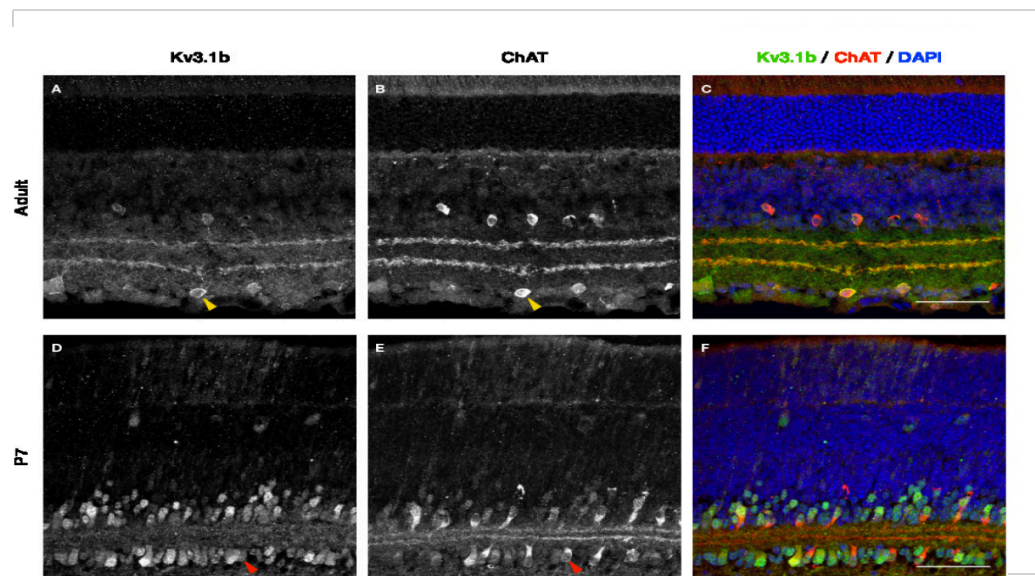




# How do SACs lose their excitability?

**Hypothesis: The expression of the potassium Kv3 channels increases upon maturation possibly leading to the loss of SACs excitability**

## Preliminary experimental exploration



(O.Marre-E. Orendorff)

### Localization of Kv3.1b in adult and P7 retinas.

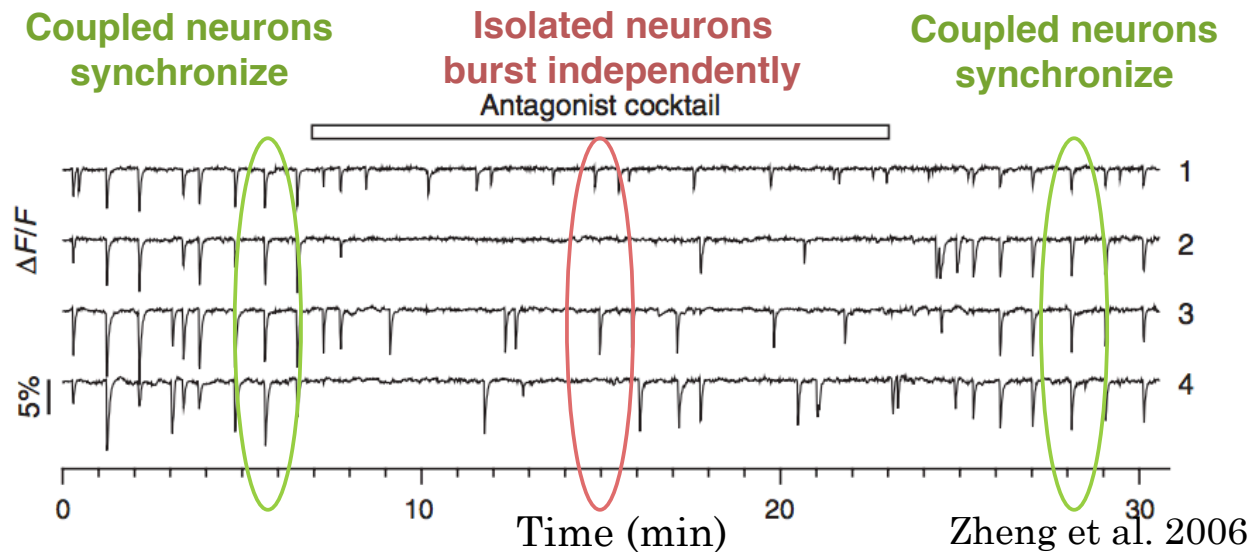
(A-C) Adult retina section showing Kv3.1b (green) and choline acetyltransferase (ChAT, red) reactivity in starburst amacrine cells. Cell nuclei stain (DAPI, blue).

(D-F) P7 retina section showing little colocalization of Kv3.1b with ChAT in starburst amacrine cells.

**However, results are preliminary as experiment is not yet conclusive**

# Cellular mechanisms of stage II retinal waves

## C. Synchrony through Acetylcholine

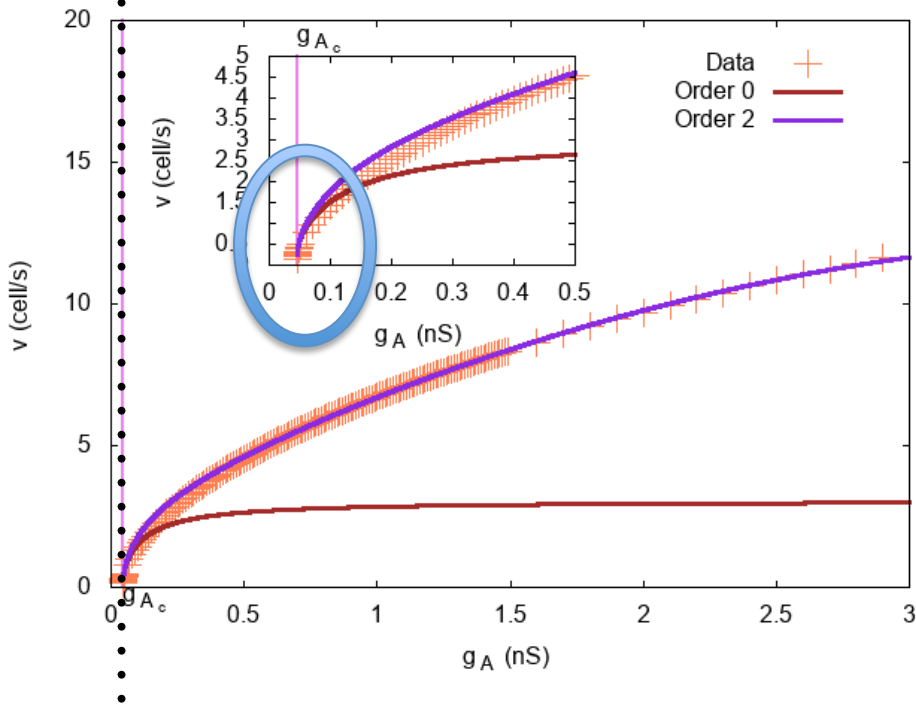


**Mutual excitatory  
connections between SACs through  
Acetylcholine**

# Waves speed

$$v_0 = \frac{1}{t_C - \frac{1}{\mu} \log \left( 1 + \frac{1}{g_A} \frac{2\mu\sqrt{\gamma_A}}{d\beta\Omega} \left( \frac{I_{SN} + g_{sAHP} R^4 (V_- - V_K)}{(V_- - V_A)} \right) \right)}$$

## Waves speed

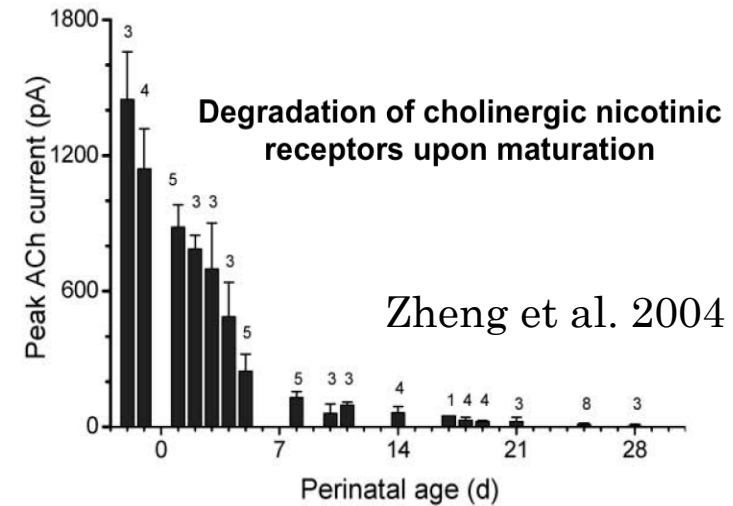


## Propagation threshold

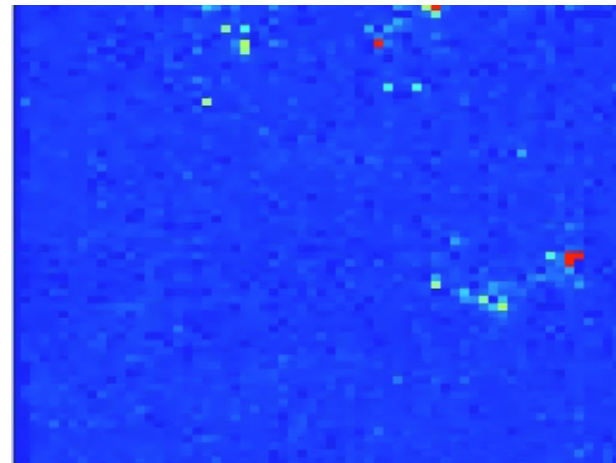
$$g_{A_c} = - \frac{2\mu\sqrt{\gamma_A}}{n_i\beta\Omega} \frac{I_{SN} + g_S R^4 (V_- - V_K)}{V_- - V_A}$$

# Variability within retinal waves

## ii) Development



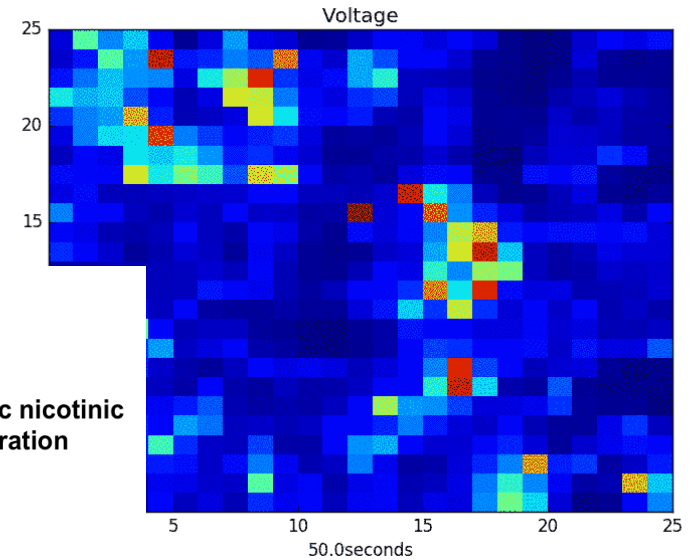
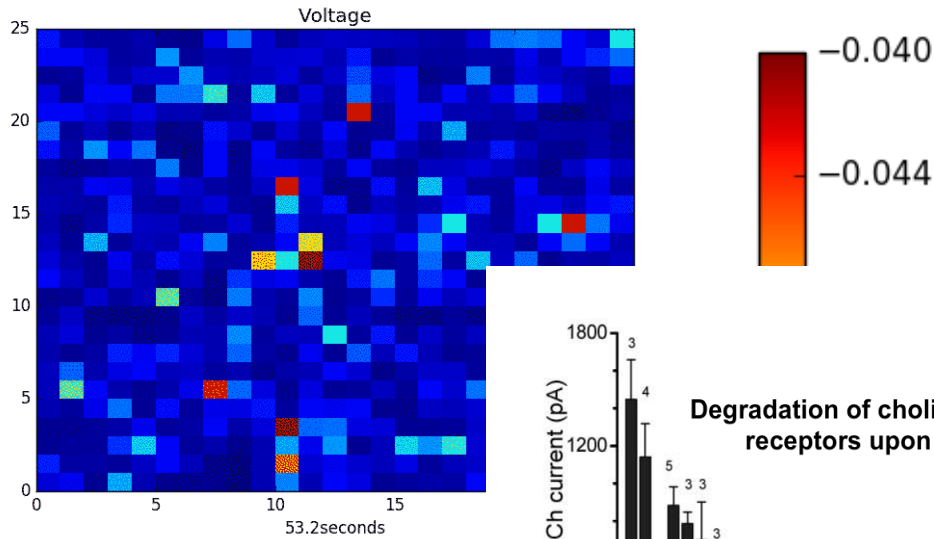
## iv) Spatial Variability



# Network of SACs : Simulated Voltage

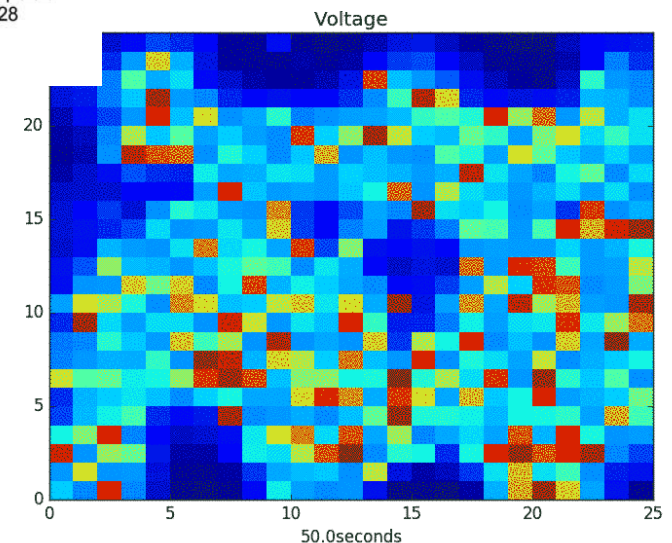
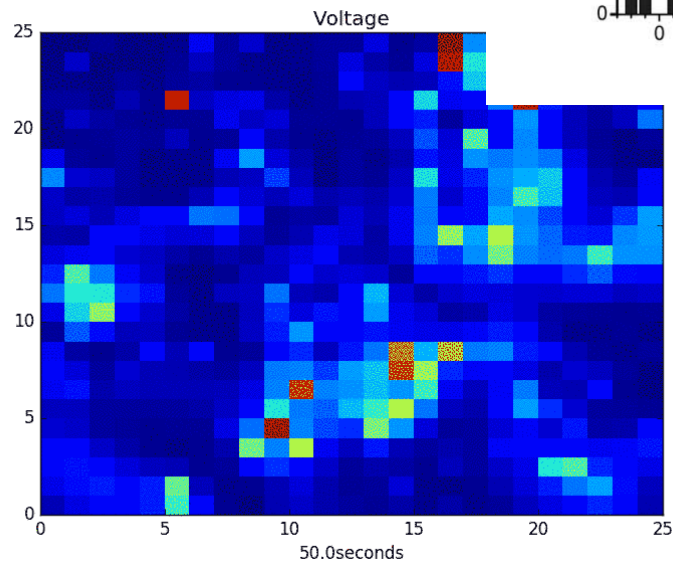
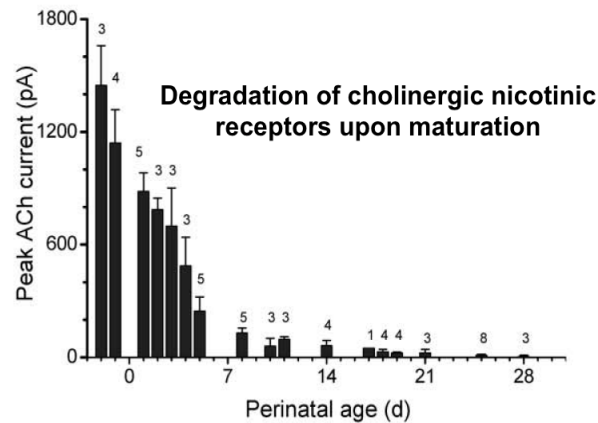
Isolated Neurons

$g_{ACh} = 0.126 \text{ nS}$



$g_{ACh} = 0.168 \text{ nS}$

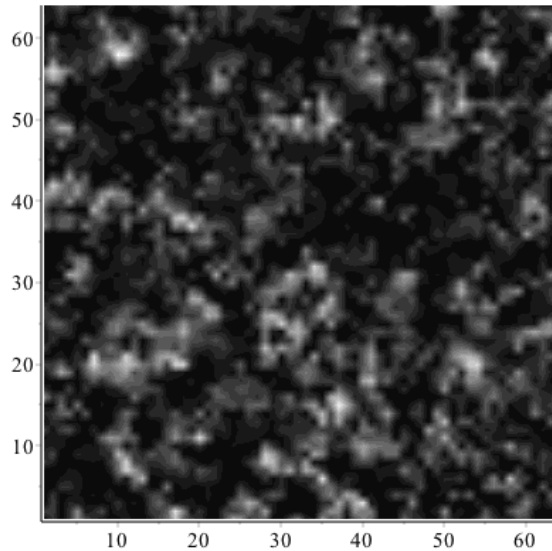
$g_{ACh} = 0.21 \text{ nS}$



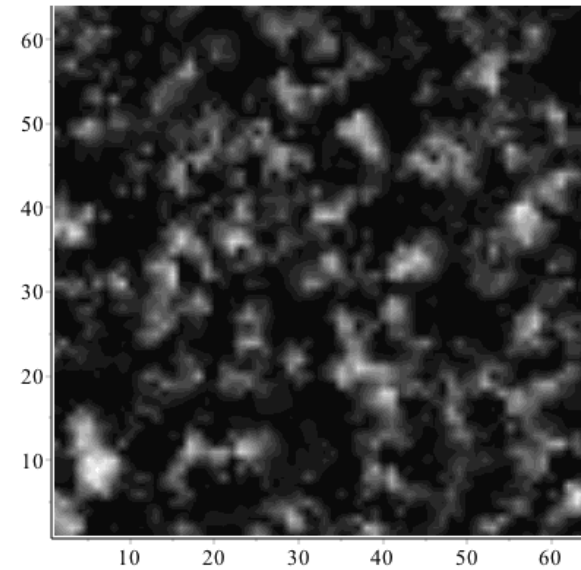


# Network of SACs : Simulated Calcium Concentration

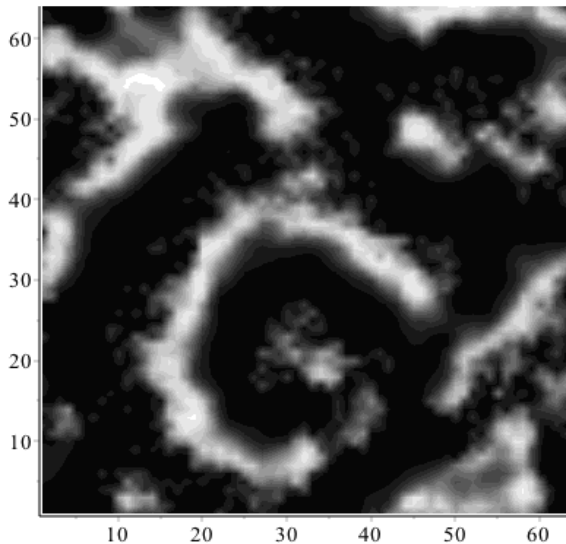
$g_{ach}=0.102$  nS



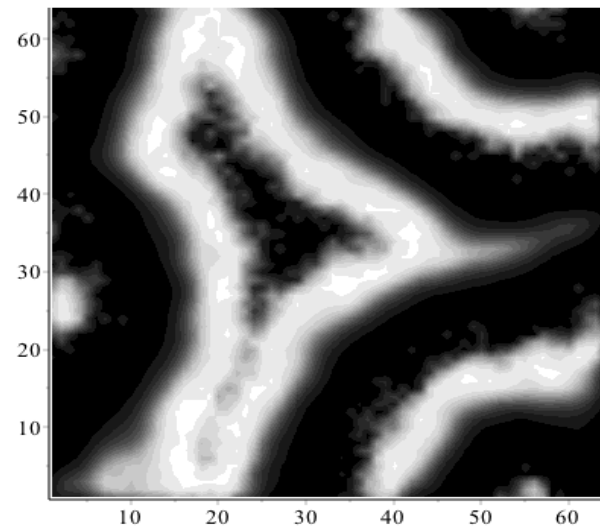
$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS



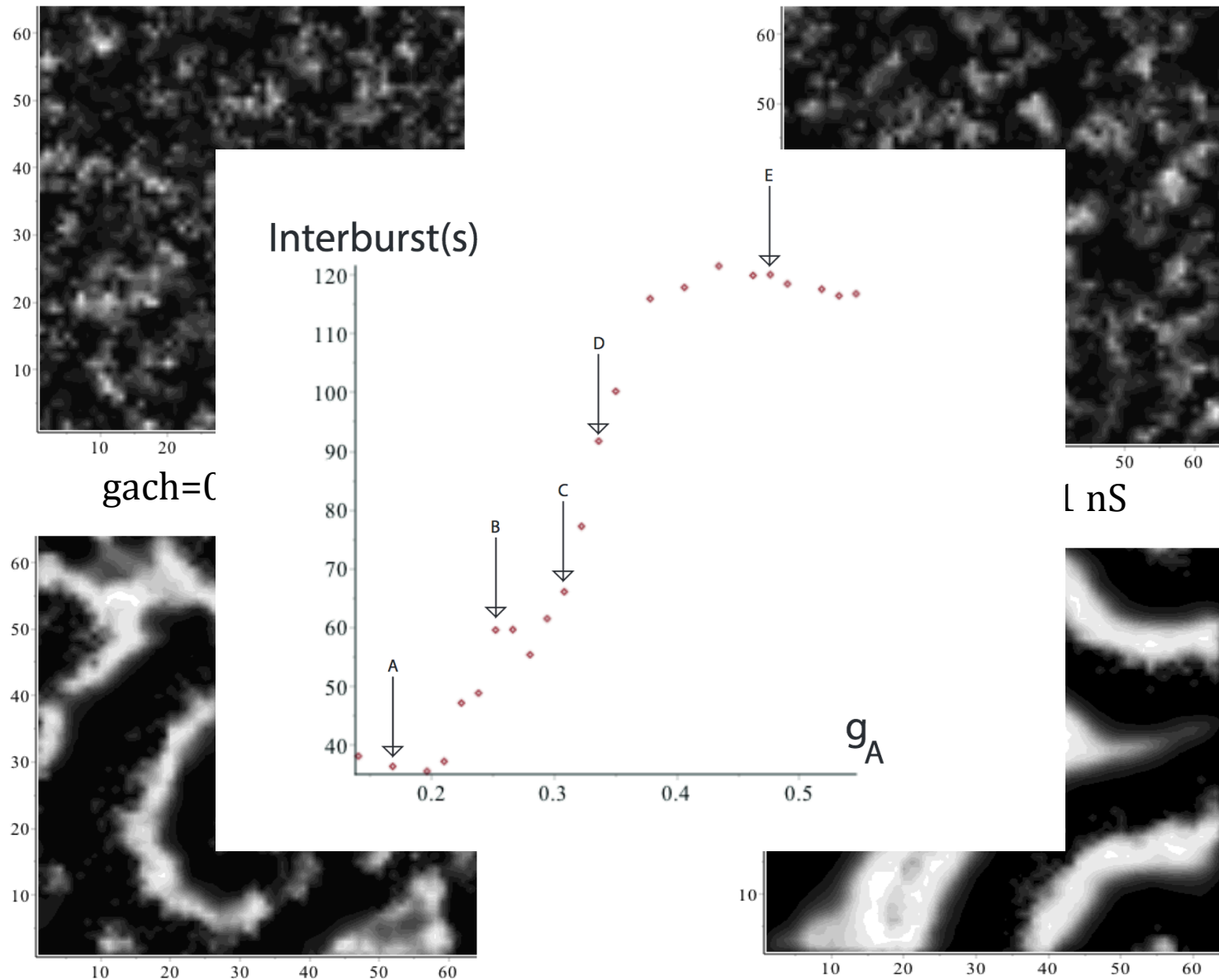
$g_{ach}=0.21$  nS



# Network of SACs : Simulated Calcium Concentration

$g_{ach}=0.102 \text{ nS}$

$g_{ach}=0.126 \text{ nS}$

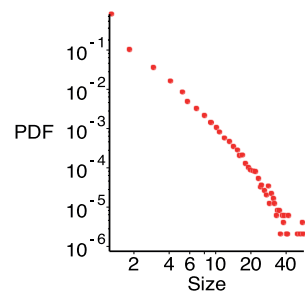
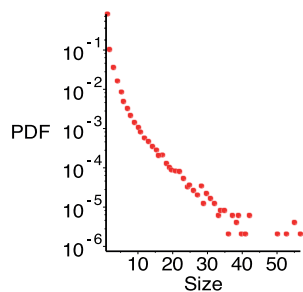


# Waves size distribution

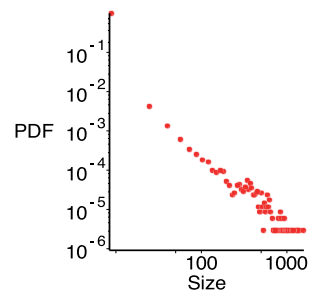
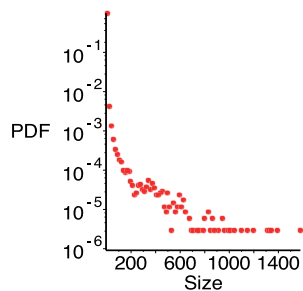
lin-log

log-log

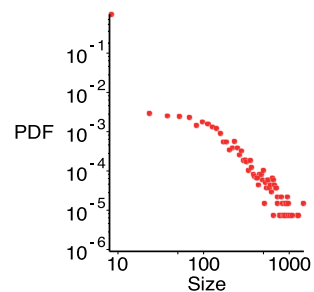
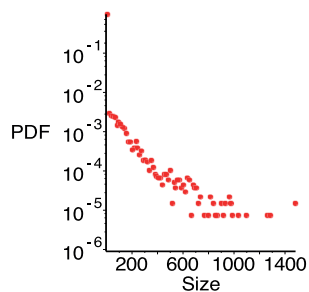
A



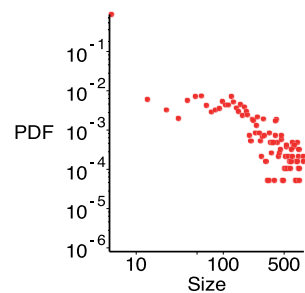
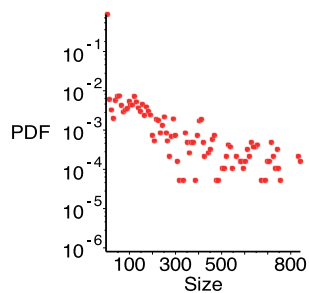
B



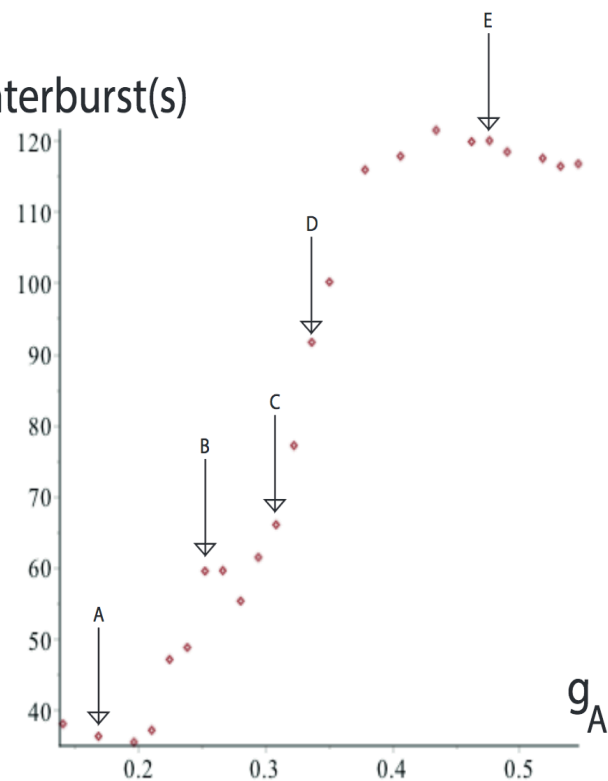
C



E



Interburst(s)



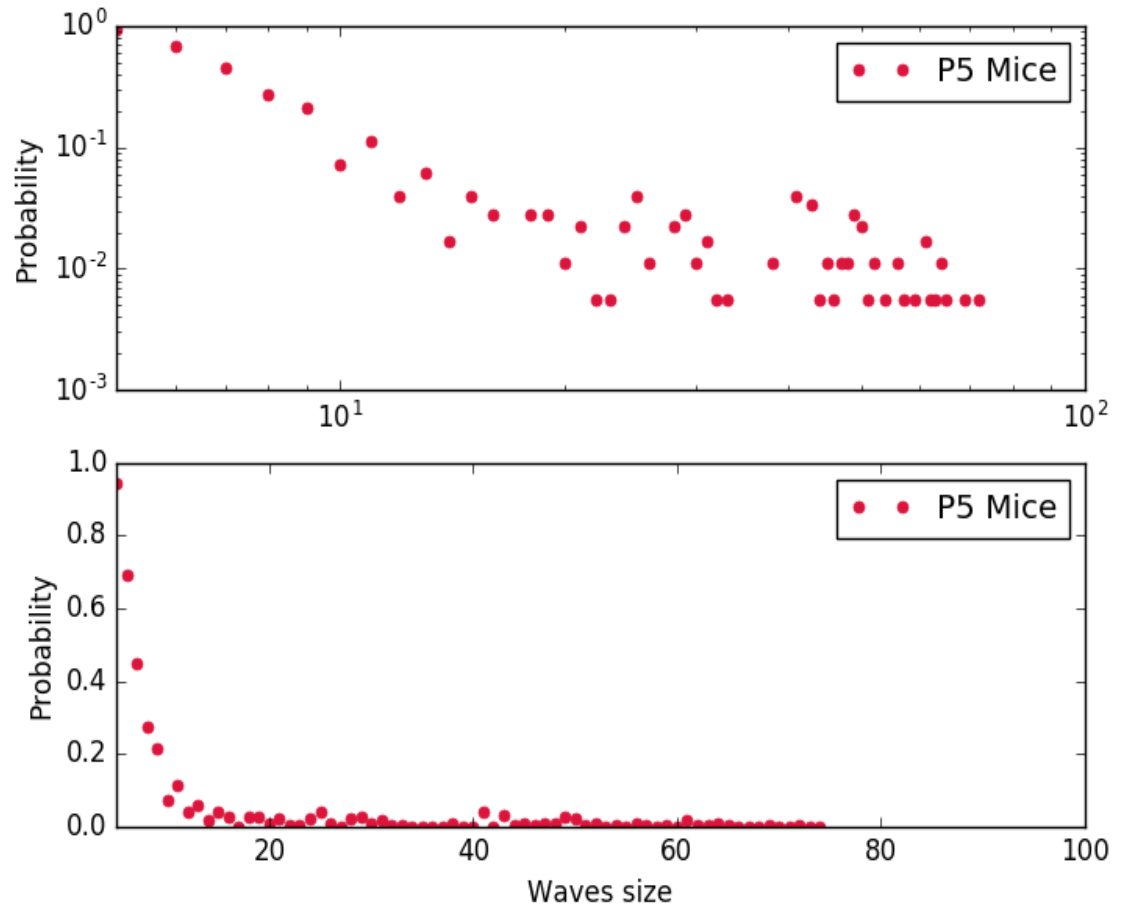


# N-neuron model

- There is a **competition** between 2 mechanisms:
  - Period variability which tends to desynchronise
  - Acetylcholine which tends to synchronise
- There is an intermediate regime of coupling, where **variability** is maximum
- Therefore there is a wide repertoire of patterns
  - **Weak coupling** leads to small **localised activity**
  - **Moderate coupling** leads to **propagating patterns**
  - **Strong coupling** leads to **complete synchrony** of neurons

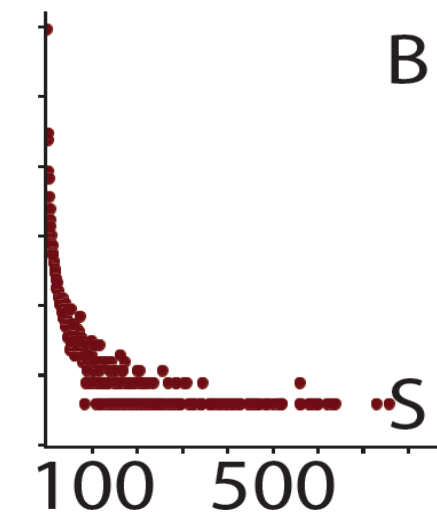
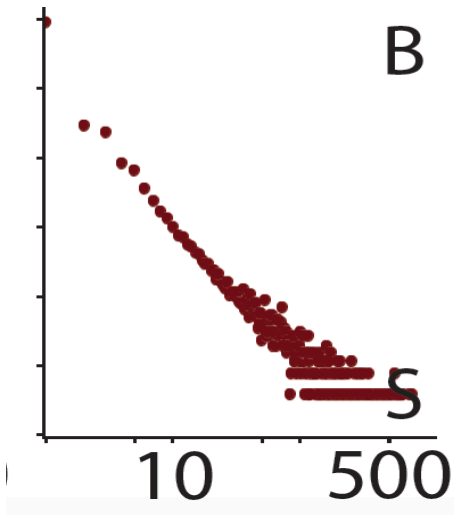
# Experimentally varying Ach conductance (Data D. Karvouniari + Institut de la Vision)

Experiment

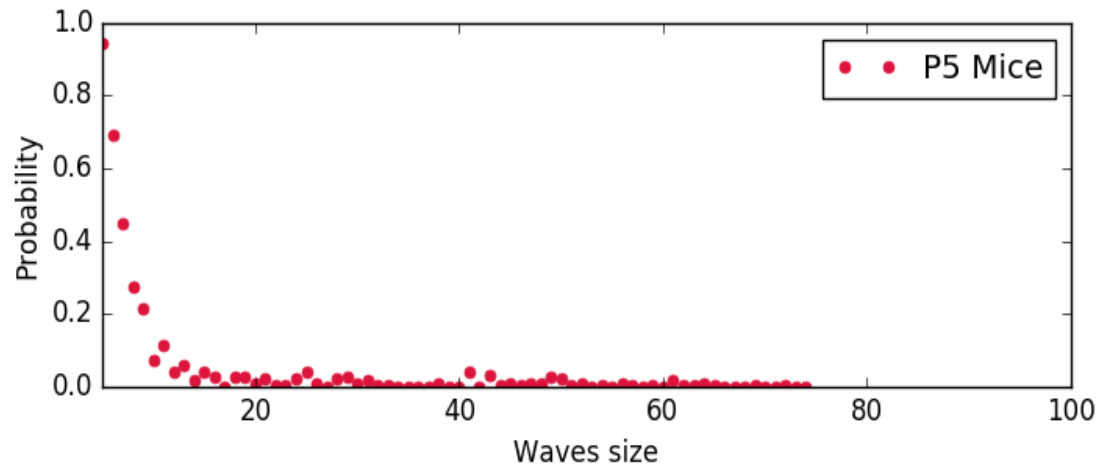
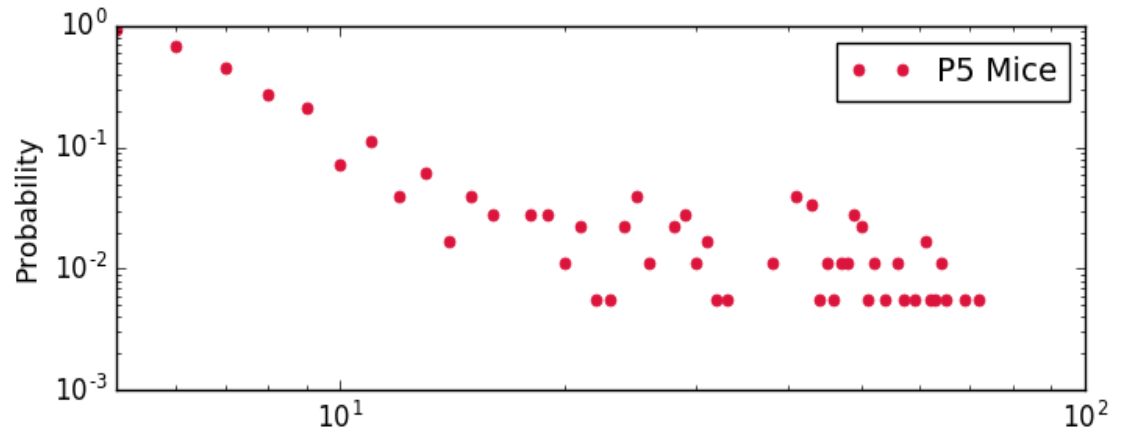


# Experimentally varying Ach conductance (Data D. Karvouniari + Institut de la Vision)

Model



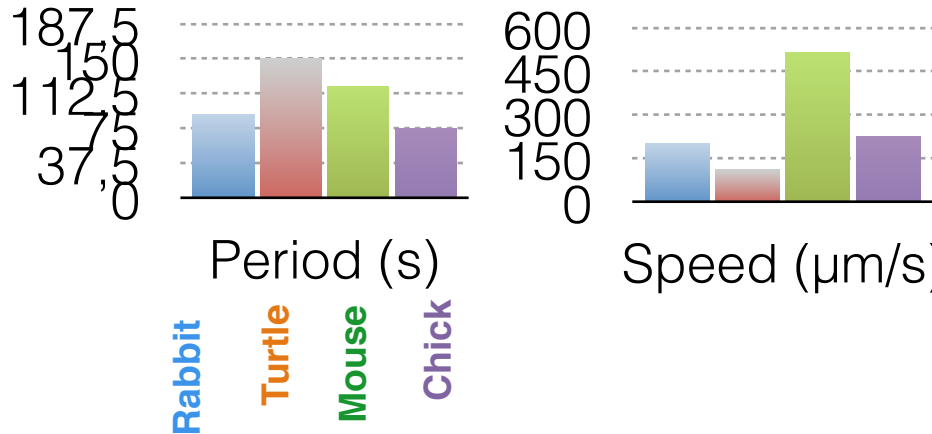
Experiment



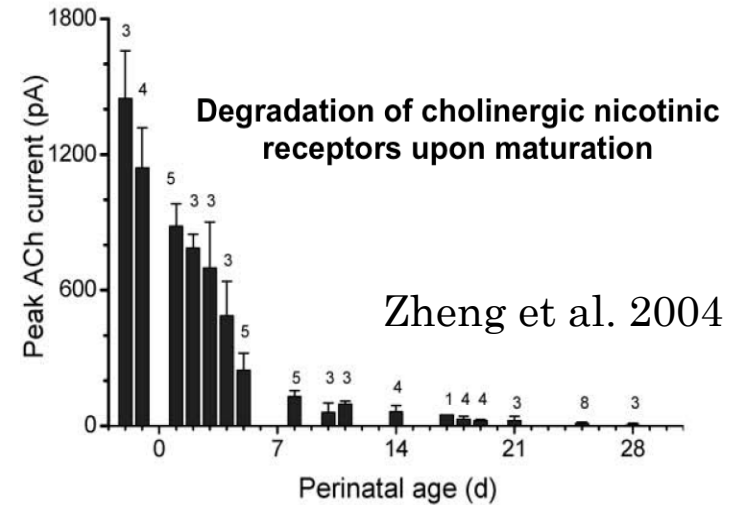
# Variability within retinal waves

## i) Across species

Godfrey et al. 2007

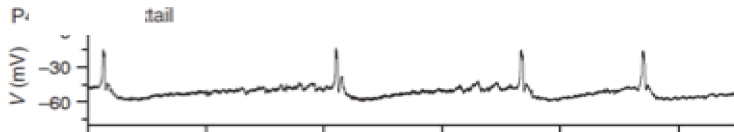


## ii) Development

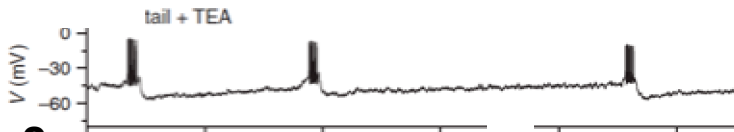


## iii) Pharmacology

P4

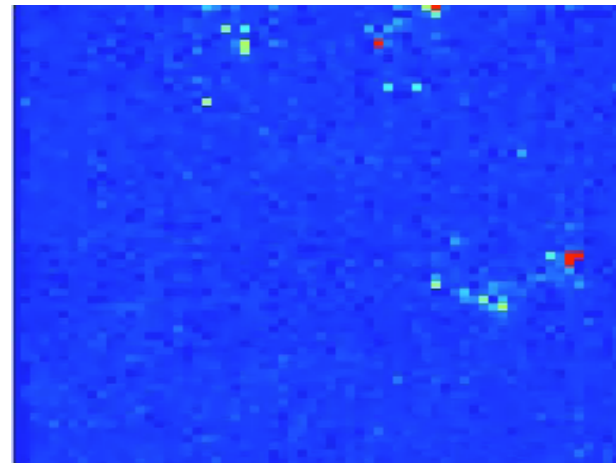


P8



0 Time (sec) 50

## iv) Spatial Variability



# Conclusion

- **Biophysical model of stage II retinal waves relevant at:**
  - The cells scale (bursting, experimental match and predictions)
  - The network scale (waves propagation)
  - The developmental level (evolution of ionic channels and synapses).
- **Theoretical description via bifurcation theory**
  - Bursting
  - Interburst variability
  - Waves patterns
- **Next step: reactivating waves in adults.**